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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/904,968	GERMINO ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006 and 06 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,16,18-25,28-37,39-42,44,48-52,55-61,76 and 78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,16,18-25,28-37,39-42,44,48-52,55-61,76 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 10/10/06. Claims 1, 2, 20, 25, 31-37, 44, 48-50, 55-57, 59, and 60, have been amended, claims 5-15, 17, 26-27, 38, 43, 45-47, 53-54, 62-75 and 77 have been canceled. Claims 1-4, 16, 18-25, 28-37, 39-42, 44, 48-52, 55-61, 76, and 78 are pending and examined in this office action. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive to place the application in condition for allowance for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. This action is **FINAL.**

Election/Restrictions

2. The first action on the merits in this application was written to address methods and products insofar as they relate to the primer pair of SEQ ID NO: 3 and 4 and the nested primer pair SEQ ID NO: 19 and 20. Further, the mutation elected for prosecution is the mutation at position 3336 of SEQ ID NO: 1, wherein the nucleotide at position 3336 is deleted (see office action mailed 1/29/04, page 2). The interview summary on 10/20/04 the examiners suggested requiring all 8 of the primer pairs in the independent claim, referring, it appears to a possible claim which requires a primer pair for the amplification of each "section" that was present in claim 5 of the claim set filed 6/10/04. Applicant's instant claims set forth in the alternative eight different primers. Where there are alternative SEQ ID NO given in a claim, the claim has been considered only insofar as it relates to the ELECTED SEQ ID NO. For example, independent claim 1 requires two primers selected from the group consisting of SEQ ID NO: 3, 4, 5, and 6, and two primers selected from the group consisting of SEQ ID NO: 19, 20, 21, and 22. This claim has been examined to consider the primers for the first amplification product to be SEQ ID

NO: 3 and 4, and the primers for the second amplification product to be SEQ ID NO: 19 and 20, as set forth by the election. Claims 25, 44 and 60 have been treated like claim 1, as they recites the primers for the method in a similar fashion. As set forth in the answer to the petition regarding restriction, should the claims directed to the elected pairs of primers become allowable, and should those claims continue to recite in the alternative the non-elected primer pairs, examination will be extended to the non-elected primer pairs.

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the specification does not provide antecedent basis for a deletion in SEQ ID NO: 1 at position 3336. The specification at page 109 discusses a deletion referred to at G3336 in exon 13, but does not ever discuss a deletion any mutation or deletion within exon 1 or the surrounding introns, especially not the deletion at position 3336 of SEQ ID NO: 1 that is set forth in claim 20.

Response to Remarks

In response to this objection, application states that the elected mutation and primers are not located in different exons as alleged by the office action (page 14 of response). This statement by applicant appears to represent a misunderstanding of the basis for the objection. The issue the examiner is attempting to address is that the specification does not provide antecedent basis for a deletion in SEQ ID NO: 1 at position 3336. The examiner understands that this position is within exon 1 of the PDK1 genes, and that a deletion at this position was set forth in the originally filed claims. The examiner also understands that the G3336 deletion discussed on page 109 of the specification is within exon 13 of the gene, and that the mutation

referred to in claim 20 is not the same mutation referred to on page 109 of the specification. This is precisely the problem. The originally filed text of the specification does not appear to discuss or mention a deletion in SEQ ID NO: 1 at position 3336, and therefore the specification does not provide proper antecedent basis for the claimed subject matter. Applicant is required to point out in the specification where antecedent basis is provided for a deletion of position 3336 of SEQ ID NO: 1 is provided or to amend the specification to provide proper antecedent basis for this claimed invention.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4, 16, 18, 19 and 20-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 16 and 19 are indefinite because the claim appears to require that the set of primers "selectively hybridize to a flanking sequence…of **each** of polycystic kidney disease-associated protein-1 (PDK1) gene sequences," but this recitation is inconsistent with the remarks filed 10/6/06 where applicant states that the set of primers selectively hybridize to "any" of the eight regions. It is not clear from the claims and prosecution history, therefore, if the claimed set must contain primers that hybridize to each possible flanking region (of which there are actually sixteen since each section is bound by two different flanking regions), to one flanking region for each segment listed, or to only some of the flanking regions. The use of the word "each" in line

three of the claims suggests that it must be one of the first two interpretations set forth above, but applicant's remarks filed with the amendments to the claim suggest that applicant intends for it to be the third option.

Claims 20-24 are indefinite over the recitation "and is about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set froth in SEQ ID NO: 1." This language is very confusing because it is not clear what applicant intends by reciting "at least 90% complementary" to two nucleotides. If two the two nucleotides are present, there is 100% complementarity, if only one is present there is 50% complementarity. Furthermore, it is not clear if the two nucleotides have to be contiguous or if they can be separated by an intervening nucleotide as they are in SEQ ID NO: 1. The claims are further indefinite because they recite "and is about..." but it is not entirely clear what "is" about 90% complementary- the ten nucleotides or the entire claimed polynucleotide. Applicant states in the remarks that accompanied this amendment that claim 20 unambiguously recites that the polynucleotide is at least ten nucleotides in length (the examiner agrees that this is required and notes that there is no upper length limitation due to the use of the transitional phrase "comprising"), and that the polynucleotide is about 90% complementary to the region containing the mutation/deletion at position 3336. The examiner does not agree that this is entirely correct because the claim does not require complementarity to a "region" but to only two nucleotides.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In claim 20, the requirement that the claimed polynucleotide comprise a sequence that is required to be about 90% complementary to only two particular nucleotides appears to be new matter. In the remarks filed with the amendment, applicant points to ¶0043 and ¶0057 as providing support for the amended claims. In ¶0043 the specification provides support for molecules that have at least about 90% identity with SEQ ID NO: 3 to 51 and 61 to 113, but this paragraph is silent as to molecules that have about 90% identity with only two particular disconnected nucleotides of SEQ ID NO: 1 generically or nucleotides 3335 and 3337 in particular. Paragraph 0057 discusses polynucleotides that are substantially identical to SEQ ID NO: 1, but again there is no discussion of a molecule that is "about 90% identical" to the complement of only two nucleotides.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 20, 21, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonczol et al. (WO 97/40165).

Gonczol et al. teach an isolated nucleic acid which comprises the nucleotide sequence 5'-AGCGCGCCGGG-3' contained within the nucleic acid encoding human CMB phosphoprotein (pp) 150 (see nucleotides 3290-3300 and 5688-5698 of the sequence given in Figure 6A and B; also see figure description, p. 4). This eleven nucleotide sequences is complementary to nucleotides 3331-3342 of instant SEQ ID NO: 1, except that the "T" at position 3336 is deleted. It therefore is 100% complementary to nucleotides 3335 and 3337 of SEQ ID NO: 1. Thus, Gonczol et al. teach an isolated polynucleotide comprising a sequence complementary to at least ten nucleotides to a nucleotide sequence of SEQ ID NO: 1, wherein the nucleotide sequence "corresponds" to nucleotide 3336 and wherein nucleotide 3336 is deleted. Gonczol et al. teach vectors and host cells comprising this sequence (p. 10, first full ¶, for example). Thus, Gonczol et al. provide nucleic acids and constructs which meet the limitations of claim 20, 21, and 22.

Applicant traversed this rejection in the remarks filed 10/20/06. Applicant argues that it appears the office action is rejecting based on the claim "substantially identical" and that this phrase has been deleted. The rejection is based upon the fact that the molecule taught by Gonczol et al. meets all of the structural limitations of the claims. The instant claims are broadly drawn using "comprising" language, and so, provided the structural features that follow the phrase "comprising" are present in the prior art molecule, that molecule can have any additional sequence 5' or 3' of the feature required to be "comprised" within the isolated polynucleotide.

As noted in the rejection, the molecule taught by Gonczol et al. comprises ten contiguous nucleotides and the ten nucleotides comprise a fragment that is 100% identical to nucleotides 3335 and 3337 of SEQ ID NO: 1.

Response to Remarks

Applicant argues that the fragments within Gonczol et al. are not "about 90% complementary to the ten nucleotide region surrounding and containing the 3336 deletion of SEQ ID NO: 1." To the contrary, the region is recited in the sequence listing as 5'-CCCGGTCGCGCT-3', that is nucleotides 3331-3342 of SEQ ID NO: 1. Without the nucleotide present at position 3336, this region is: 5'-CCCGGCGCGCT-3'. The complement of this region is thus 5'-AGCGCGCCGGG-3'. The sequence taught by Gonczol et al. is 5'-AGCGCGCCGGG-3', which is identical to the complement of the region with 3336 deleted. Thus, the molecule taught by Gonczol et al. COMPRISES precisely what it appears that applicant is attempting to claim. The rejection is applied to the amended claims.

9. Claims 20, 23, and 24 rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US 5474796).

Brennan provide an array, which is a solid matrix, having thereupon every possible 10-mer nucleic acid in a separate position on the array (see Example 4, Col. 9). Thus, Brennan provides each possible isolated polynucleotide of ten nucleotides in length, including any that are within the scope of instant claim 20. With regard to claim 23, these nucleic acids are all immobilized on a solid matrix, and with regard to claim 24, there are a plurality of nucleic acids on the solid matrix which meet the limitations of claim 20.

Response to Remarks

Applicant argues that Brennan is not enabling because Brennan does not teach primers which detect a mutation/deletion in a PKD1 gene. The instant claim does not recite a primer. Brennan exemplifies making every single possible nucleic acid of ten nucleotides in length, and thus teaches every possible molecule of ten contiguous nucleotides that is within the scope of the instant claims. The rejection is applied to the amended claims.

10. Claims 20, 23, and 24 rejected under 35 U.S.C. 102(b) as being anticipated by Chee et al. (US 5837832).

Chee et al. provide an array, which is a solid matrix, having thereupon a variety of nucleic acids, one of which is their SEQ ID NO: 183. Their SEQ ID NO: 183 is ten contiguous nucleotides and comprises the sequence "CG" which is 100% complementary to nucleotides 3335 and 3337 of SEQ ID NO: 1 (which are G and C, respectively). The claim as it is written is extremely broad requiring only that the claimed molecule comprise ten nucleotides and that it is about 90% complementary to nucleotides 3335 and 3337 of SEQ ID NO: 1. The molecule taught by Chee et al. meet these limitations. With regard to claim 23, these nucleic acids are all immobilized on a solid matrix, and with regard to claim 24, there are a plurality of nucleic acids on the solid matrix, one of which is their SEQ ID NO: 183 (see Col. 14-16).

Response to Remarks

The rejection is modified to address the amended claim, nonetheless applicant's remarks regarding this reference are addressed. The sequence for SEQ ID NO: 183 of Chee et al. is 5'-GGCCCGGAGC-3' and this sequence is 90% identical to nucleotides 3329- 3339 of instant SEQ ID NO: 1, wherein the "T" at position 3336 is deleted. It is agreed that the molecule taught by Chee et el. is not 90% **complementary** to a ten nucleotide region overlapping with nucleotide

3336 of SEQ ID NO: 1, but such a molecule is not required by the claims. The rejection addresses the breadth of the claim and why the Chee et al. disclosure continues to meet the limitations of the claims.

Claim Rejections - 35 USC § 112

11. Claims 1-4, 16, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claim 1 is drawn to a set of primers which comprises primers that selectively hybridize under highly stringent conditions to a nucleotide sequence which flanks a series of portions of instant SEQ ID NO: 1, which is the human polycystic kidney disease-associated protein gene sequence. The claim requires that the primers comprise a 5' region which can hybridize to both PKD1 and "a PKD1 gene homolog" and a 3' region that selectively hybridizes to a PKD1 gene sequence but not to the gene homolog. Instant claim 1, as elected, requires instant SEQ ID NO: 3, 4, 19, and 20. Of these, only instant SEQ ID NO: 3 is identified in the specification as being a "PKD1 specific primer" (see Table 1, p. 103 of the specification). The specification identifies eight additional primers as being PKD1 specific, that is instant SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18. The scope of the claim is very broad with regard to the identity of the required primers that contain portions that hybridize to PKD1 but not to PKD1 homologues, since the

claim appears to require at least one primer flanking each region of SEQ ID NO: 1 recited in the claim, but only a single primer which meets the requirements given in the claim is set forth, namely SEQ ID NO: 3. These primers can possibly be chosen from anywhere within the flanking regions of the segments recited in claim 1, but there is no guidance in the specification as to which regions are unique to PKD1 relative to the undefined homologs.

The specification provides an over fifty kilobase nucleic acid sequence (instant SEQ ID NO: 1) which it teaches is a "wild-type" PKD1 gene sequence (¶0054). The specification does not provide the nucleic acid sequence of any "PKD1 gene homolog" nor does the specification provide a definition of what structural features identify such a homolog. The specification teaches that the sequence of PKD1 was aligned with that of two homologues present in GenBank record AC002039 (¶0223). The prior art record does not annotate the presence of the homologues. The identity of the nucleic acid sequence of PKD1 homologues is essential for the practice of the claimed invention, as one would need the nucleic acid sequence of these homologues to in order to select additional members of the claimed set of oligonucleotide primers. Roelfsema et al. teach a model of repeated structure of PKD1 gene on chromosome 16, teaching a repetition iteration of at least six times, and states that the precise number of repetitions is unknown (1997, as cited in IDS, see Figure legend). In addition, the post-filing date art teaches that there are at least four additional homolog sequences of PKD1 on human chromosome 16p13.1, all with a high degree of identity to SEQ ID NO: 1, and that the exact number of the homologous genes as well as their structure is yet unknown (Bogdanova et al. Genomics, 2001, see first page and throughout). Bogdanova et al. continues by stating "the accumulation of precise sequence information on the HG is desperately required to design

PKD1-specific reagents that would serve more conventional scanning techniques (p. 334, first column)." Thus, the claims encompass primers which are designed to exclude the amplification of nucleic acid homolog sequences that were not described at the time the invention was made, and that are not described in the instant specification. There is no guidance in the specification as to how to look at instant SEQ ID NO: 1 and to select, of all of the possible primers (millions of possible primers within SEQ ID NO: 1) which ones would meet the functional requirements set forth by the claims, and thus could be included within the set of claimed primers.

Response to Remarks

Applicant traverses the rejection beginning on page 24 of the response.

Applicant teaches that the presence of PKD1 homologues on chromosome 16 was well known by Applicants as well as other skilled artisans. Be that as it may, the identification of these molecules as well as the knowledge of regions of differences between these molecules and the "wild type" PKD1 is critical to the description of the claimed invention. The MPEP states "A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. In re Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." In this case, the essential novelty of the claimed set of primers includes the requirement that they contain 3' sequences that selectively hybridize to a PKD1 gene sequence and not to a PKD1 gene

homolog sequence. In this case, with the exception of a single primer, SEQ ID NO: 3, the claim requires primers that are not structurally defined in the claim, only defined as to their function. Applicant cannot incorporate by reference from non-patent literature what is essential to practice the claimed invention. Even if the sequences were part of the specification, however, this does not remove the breadth of the claims relative to the particular teachings of the specification. The fact that one might be able to identify sequences within SEQ ID NO: 1 is immaterial to the question of written description. Here, a particular functional requirement is set forth for the claimed primers, but no written description of primers that meets the functional requirement for each of the sixteen flanking regions is present. It is not enough to provide a large unannotated nucleic acid sequence and claim the claimed primers can be identified within the large sequences, written description requires a description of what is claimed. The rejection is maintained.

12. Claims 20-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to isolated polynucleotides and constructs comprising polynucleotides, wherein the polynucleotide comprises a contiguous sequence of at least ten nucleotides with no specific requirement as to the identity of the ten nucleotides, except that claim 20 further recites the ten nucleotides is "about 90% complementary to at least nucleotide

335 and 337" of SEQ ID NO: 1. The claim is indefinite, but it appears that applicant may be trying to claim a fragment of SEQ ID NO: 1 wherein position 3336 has been deleted. The claim language is extremely broad. The claim requires that the claimed polynucleotide comprises at least ten nucleotides that are where two of them are from SEQ ID NO: 1. Thus, the claim encompasses a polynucleotide that is at least 10 nucleotides in length and which has the complements of nucleotides 3335 and 3337 of SEQ ID NO: 1. And the claims are broadly drawn using the claim language "comprising" which means that this broadly set forth ten nucleotide structure can be contained within any possible sequence context of any length. Thus, the claims are extremely broad in nature and encompass polynucleotides of millions of possible origins and identities, including genes and gene fragments that have very little structural and no functional relationship to instant SEQ ID NO: 1. The specification describes instant SEQ ID NO: 1, and therefore molecules consisting of fragments from within instant SEQ ID NO: 1 are described. The originally filed claims further teach a deletion of a single nucleotide from position 3336 of SEQ ID NO: 1 (pertaining to the elected invention), so nucleotide fragments that consist of fragments of instant SEQ ID NO: 1 except that the nucleotide at position 3336 is deleted are also described. However, given the limited disclosure of the specification and given the extremely broad nature of the claimed invention, it is concluded that the claimed invention is not supported with proper written description.

Response to Remarks

Applicant traverses the rejection, pointing to the amendments to the claims. The amended claim and the breadth of the claim is analyzed in the rejection. It is reiterated that the

requirement that the claimed polynucleotides is 90% complementary to two nucleotides is still very broad in nature, leaving the identity of eight nucleotides plus any additional nucleotides open. The rejection is applied to the amended claim.

13. Claims 1-4, 7, 16, and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for primers having SEQ ID NO: 3, 5, 8, 10, 11, 14, 16, and 17, which can be used to specifically amplify PKD1 gene having SEQ ID NO: 1 and not PKD1 gene homologs, does not reasonably provide enablement for additional primers that have this property. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. Claims 20-24, 28-37, 39-42, 44, 46-52, 55-61, and 76-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

Independent claim 1 is drawn to a set of primers which comprises at primers that selectively hybridize under highly stringent conditions to a nucleotide sequence which flanks a series of portions of instant SEQ ID NO: 1, which is the human polycystic kidney disease-associated protein gene sequence. The claim requires that the primers comprise a 5' region which can hybridize to PKD1 and optionally "a PKD1 gene homolog" and a 3' region that selectively hybridizes to a PKD1 gene sequence but not to the gene homolog. Instant claim 1, as

elected, requires instant SEQ ID NO: 3, 4, 19, and 20. Of these, only instant SEQ ID NO: 3 is identified in the specification as being a "PKD1 specific primer" (see Table 1, p. 103 of the specification). The specification identifies eight additional primers as being PKD1 specific, that is instant SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18. The scope of the claim is very broad with regard to the identity of the required primers that are contain portions that hybridize to PKD1 but not to PKD1 homologues, since of these only one is identified by the recited SEQ ID NO: 3. These primers can possibly be chosen from anywhere within the disclosed "flanking regions" of the fragments of nucleotide sequence of instant SEQ ID NO: 1, but there is no guidance as to which regions are unique to PKD1 relative to the undefined homologs. Further, the specification does not provide any clear definition of how much sequence difference is necessary between two molecules for one to be a "homolog" of the other, as opposed to one being a polymorphic variant of the other. Thus, for these product claims the nature of the invention depends on the ability to identify primers which meet the functional characteristics set forth in the claims.

The scope of independent claim 20 is previously discussed in this office action. The claim language is extremely broad. Thus, the claims are extremely broad in nature and encompass polynucleotides of millions of possible origins and identities, including genes and gene fragments that have very little structural and no functional relationship to instant SEQ ID NO: 1. Thus, the nature of the invention in this case, first involves the ability to synthesize the claimed molecules, but second requires a knowledge of how to use those molecules.

The remaining claims are method claims, and recite amplification steps which eventually lead to "identifying the presence or absence of a mutation in the PKD1-specific amplification

product, thereby detecting the presence or absence of a mutation in the PKD1 polynucleotide in the sample," with claim 44 and 60 reciting that the mutation identifies subjects at risk for a PKD1 associated disorder or diagnoses such a disorder in a subject. The claims encompass the identification of a mutation at any position within the amplified products, which given the elected primer sequences encompass possible mutations at 2300 possible nucleotides. Regarding claims 25 and those that depend from them, these claims do not recite an association with a disease, but in the nature of the method requires such a knowledge in order for the method to be "used." While one could practice the method, at least with regard to the single disclosed mutation in this amplification product, one would not know how to "use" the method as the specification does not set forth the relationship between the deletion at nucleotide 3336 and any PKD1 related disorder.

Teachings in the specification and the prior art

The specification provides an over fifty kilobase nucleic acid sequence (instant SEQ ID NO: 1) which it teaches is a "wild-type" PKD1 gene sequence (¶0054). The specification does not provide the nucleic acid sequence of any "PKD1 gene homolog" nor does the specification provide a definition of what structural features identify such a homolog. The specification teaches that the sequence of PKD1 was aligned with that of two homologues present in GenBank record AC002039 (¶0223). This record does not annotate the presence of the homologues, nor is any other guidance or source given in the specification or the prior art as to how the location of these "homologs" within prior art sequences. The identity of the nucleic acid sequence of PKD1 homologues is essential for the practice of the claimed invention, as one would need the nucleic acid sequence of these homologues to in order to select additional members of the claimed set of

oligonucleotide primers. Roelfsema et al. teach a model of repeated structure of PKD1 gene on chromosome 16, teaching a repetition iteration of at least six times, and states that the precise number of repetitions is unknown (1997, as cited in IDS, see Figure legend). The art teaches that there are at least four additional homolog sequences of PKD1 on human chromosome 16p13.1, all with a high degree of identity to SEQ ID NO: 1, and that the exact number of the homologous genes as well as their structure is yet unknown (Bogdanova et al. Genomics, 2001, see first page and throughout). Bogdanova et al. continues by stating "the accumulation of precise sequence information on the HG is desperately required to design PKD1-specific reagents that would serve more conventional scanning techniques (p. 334, first column)." Further, Phakdeekitcharoen et al. discuss the problem with selecting specific primers for the PKD1 gene, teaching that the PKD1 gene has several relevant features that make it difficult to study the PKD1 gene using molecular biology techniques, including high GC content, the lengthy coding sequence, the presence of homologs with high sequence identity and the presence of an unusual element within the gene that includes a high degree of polypyrimidines. The art recognizes that working with this gene is highly unpredictable. In such a highly unpredictable setting, a high degree of guidance is required to practice the claimed invention. Thus, the claims encompass primers which are designed to exclude the amplification of nucleic acid homolog sequences that were not described at the time the invention was made, and that are not described in the instant specification. There is no guidance in the specification as to how to look at instant SEQ ID NO: 1 and to select, of all of the possible primers (millions of possible primers within SEQ ID NO: 1) which ones would meet the functional requirements set forth by the claims, and thus could be included within the set of "at least 8" claimed primers.

Regarding claim 20, The specification describes instant SEQ ID NO: 1, and therefore fragments consisting of instant SEQ ID NO: 1 are described. The specification further teaches a deletion of a single nucleotide from position 3336 of SEQ ID NO: 1 (pertaining to the elected invention), so nucleotide fragments that consist of fragments of instant SEQ ID NO: 1 except that the nucleotide at position 3336 is deleted are also described. However, given the limited disclosure of the specification and given the extremely broad nature of the claimed invention, it is concluded that the claimed invention is not supported with proper written description.

The specification does not provide any discussion about a mutation at position 3336 of instant SEQ ID NO: 1. This mutation would be within the exon 1 or the surrounding introns, and the specification does not make any mention of such a mutation. The specification does not provide any data which suggests a relationship between this mutation and any possible PKD1 related disease or disorder. Regarding the method claims, the specification does teach and exemplify that it is unpredictable whether mutations or polymorphisms in the PKD1 gene will be associated with disease, specifically teaching in ¶ 0054 that not all nucleotide variations in SEQ ID NO: 1 will correlate with the signs and symptoms characteristic of a PKD1 associated disorder, and indeed the specification exemplifies in Table 2 that some mutations discovered segregate with disease and some do not. Thus, of all of the possible mutations that might be identified within the regions amplified in the rejected method claims, it is highly unpredictable which ones will be associated with disease. The specification has not provided a single mutation within this region that appears to be prognostic of, let alone diagnostic of disease. It is highly unpredictable whether or not such a mutation exists in this amplified region, and it is highly unpredictable whether one could identify such a mutation.

Quantity of experimentation

The quantity of experimentation required to practice the claimed invention, given the high degree of unpredictability in this art area is enormous. For the claims drawn to primer pairs, in order to practice the invention, one would have to undertake substantial trial and error experimentation to determine which possible primers, other than those comprising the SEQ ID NO: specifically given in the specification, would meet the functional requirements set forth in the claims. This would involve the synthesis of primers, but also extensive experimentation to determine if the synthesized primers are specific to PKD1 and not to PKD1 homologs. Given the fact that there is no clear disclosure of what structural features define the PKD1 homologs in the specification, nor any requirement which indicates how much sequences have to differ from instant SEQ ID NO: 1 to be considered a homolog, and the disclosure in the prior and post filing date art that there are at least six different homologs but maybe more which are unidentified, this work would require extensive experimentation. For claims 20-24, the use of the claimed invention would require extensive and entirely unpredictable work to determine if an association exists between the deletion at position 3336 of SEQ ID NO: 1 and any relevant phenotype, though the claims do not require such a use, the use of a molecule which comprises this deletion would require such knowledge. Regarding the method claims, one would have to undertake extensive studies to first identify potential mutations or polymorphisms within the amplified region, other than the single disclosed example. Whether or not such polymorphisms or mutations exist is itself highly unpredictable, and if they do exist, the location and structure of these variants is highly unpredictable. Once mutations are identified, one would have to undergo further case controlled studies in patient and control populations to determine if the

variants are predictive of any disease phenotype, and if so, which of the possible "PKD1 associated disorders" are predicted by the newly discovered mutation.

Conclusion

Thus, having carefully considered each of these factors, it is concluded that it would require undue experimentation to make and use the claimed invention commensurate in scope with claims 1-4, 7, and 16-19, and to make and use the remainder of the rejected claims.

Response to Remarks

Applicant first provides arguments directed towards claims 1-4, 7, and 16-19.

Applicant argues on pages 32-33 of the response that there is sufficient guidance because the nature of the claims, disclosure and the art available at the time of filing provide sufficient guidance as to the regions which are unique to PKD1 relative to the undefined homologs. However, this is not persuasive, because as previously discussed in this office action, the specification does not provide any specific guidance as to what additional primers can be made that meet the functional requirements of the claims. The fact that applicant refers to the homologs as "undefined homologs" underscores the unpredictable nature of this endeavor. This is complicated by the fact that the specification does not provide specific guidance as to what positively identifies a molecule as a "PKD1 homolog." In response to this concern applicant explains that one skilled in the art would not be able to determine whether the deletion/mutation 3336 is a polymorphism but that does not take away from the fact that it is an alteration in the genetic material. This argument does not address the fact that the specification does not provide clear guidance as to how to identify a particular stretch of DNA as a "PKD1 homolog." This

guidance is critical in order for one to begin to make primers that meet the limitations of claim 1 and dependents.

Applicant points out that one can compare SEQ ID NO: 1 with PKD1 homologs on chromosome 16. However, this is simply an invitation for one to attempt to identify the homologs, align the sequences, select regions of mismatch, and carry out what applicant sets forth in the specification as being the inventive process. This process is riddled with many unpredictable aspects, as discussed in the rejection.

Applicant submits that it is not necessary or relevant to the practice of the claimed invention to define how much sequence difference (or even similarity) is necessary for one to be a homolog of another. However, the examiner disagrees since the invention requires primers that distinguish homologs from PKD1 genes, it is critical to be able to identify a homolog, yet no guidance as to how to do so is provided in the specification.

Applicant states that since they disclose SEQ ID NO: 3, 5, 8, 19, 11, 14, and 16 they teach exactly how to make or use the invention (page 34). Applicant teaches how to make these precise primers, but these are not commensurate in scope with the claims, as discussed in the rejection. Sets of primers that require these particular primers are considered within the scope of the enabled invention. What is problematic in these claims is the use of broadly stated functional language to attempt to claim sets of primers which define the included members of the set only by their functional properties, in view of the factors discussed in the rejection.

Applicant cites a post filing date and states that one of skill in the art would look to the prior art for guidance. As discussed in the rejection, however, the prior art established that amplification methods which differentiated between PKD1 and its homologs were unpredictable

because it was unpredictable how to actually design the primers for such assays. Applicant's discussion of page 35 of the known mutations of the PKD1 gene is not germane to the subject of the scope of the claims with regard to the claimed primers as the product claims related to the primers do not mention mutations.

Applicant points out that the skilled artisan would not look to Applicant's disclosure to provide every operable species; no such requirement has been made. However, for the reasons of record it is maintained that it would require undue experimentation make sets of primers commensurate in scope with the claimed invention.

Applicant argues that the amount of experimentation is not enormous. This is only one factor which was used to lead to the conclusion of undue experimentation to practice the claimed invention commensurate in scope with the claims. Example 1 states that primers were selected by alignment but does not provide the alignment or even all of the sequences aligned, only specific examples in only eight of the possible sixteen flanking regions set forth in claim 1. The specification is devoid of particular guidance as to how the specific examples (that is the specific SEQ ID NO) can be modified while still retaining their inventive properties, and is silent as to additional primers in any of the sixteen possible flanking regions that would function as required by the claims. For one to identify homologs, align them and select, test, and screen additional primers is to require one to practice the same process as applicants- that is to reinvent applicant's inventive process and to invent more operable embodiments. The general concept of selecting primers that hybridize to PKD1 but not homologs was known at the time the invention was made (see àpplicant's discussion of prior art in the specification and remarks), but applicant still asserts that the primer SEQ ID NO: 3 is inventive, and the examiner agrees, because the selection of

these primers is not trivial. As discussed at length in the rejection, this is a highly unpredictable technology regarding the particular problem that is the subject of the claimed invention. For these reasons, it is not "routine" to select other primers that meet the limitations of claim 1. The rejection is maintained.

Applicant also traverses the enablement rejection of claims 20-24, 28-37, 39-42, 44, 46-52, 55-61, and 76-78.

The rejection has been modified to address amended claim 20 (remarks p. 37-38).

On page 38 applicant states that the deletion mutation at position 3336 of SEQ ID NO: 1, referring to Example 2 of the present application. This example does not mention a mutation at 3336 of SEQ ID NO: 1 which is within exon 1 (remembering that SEQ ID NO: 1 is the genomic sequence). The mutation referred to in Example 2 is at position 3336 of the coding sequence and within exon 13 (¶ 0234). There is no discussion of the mutation at position 3336 of SEQ ID NO: 1, within exon 1 of the PKD1 gene, and thus, there is no evidence in the record that this deletion was detected in a human with or without ADPKD, or any other species of animal.

Applicant further traverses the rejection of claims 25, 44, and 60, as well as those claims dependent therefrom.

It is agreed that the amendment to claims 44 and 60 significantly narrows the scope of these claims with regard to the disease detected. However, the scope of the claims are all still quite broad with regard to the specific mutation which is detected as indicative of the disease. In the amended claims, this mutation must be within the amplified sequence, which, for the elected invention is a portion of exon 1 (see Tables 1 and 2 of the specification for the targets of the elected sequence).

Applicant's arguments in the first full paragraph are not directed towards the instantly claimed invention which requires only the amplification of only a part of exon 1. While it is true that the ability to amplify a portion of exon 1 of the PKD1 gene makes it easier to detect mutations, neither the specification nor the claims nor the prior art provide a single mutation which has ever been detected in the human PKD1 gene within the region which is required to be amplified by the claims. The practice of the claimed methods requires the discovery of these putative mutations in the amplified region, and the association of these mutations with the disease. This is a highly unpredictable endeavor.

There is no teaching in the specification of any mutation that was detected within the region of nucleic acid amplified by SEQ ID NO: 3 and 4 and then further by SEQ ID NO: 19 and 20 as set forth in the claimed methods. The general disclosure of mutations in the gene in the prior art does not enable the particular claim to detecting mutations in a particular region that are associated with ADPKD. There is no evidence on the record which supports applicant's suggestion that mutations within the particularly amplified region are predictable. Again, it is pointed out that the specification must be enabling for the claimed invention, and Applicant cannon rely on the prior art to provide what is critical to the practice of the invention. In this case, a very specific fragment of nucleic acid is amplified in the claimed methods, and then the methods require identifying the presence or absence of "a mutation" an entirely undefined mutation in the sample, with many claims stating that the mutation is indicative of disease. However, there is no guidance as to the identity of the mutation to be detected, save the single mutation disclosed in the originally filed claims as being a deletion at 3336 of SEQ ID NO: 1. The specification itself, particularly the examples, is silent as to any evidence that this deletion

was detected in a human with ADPKD, or any other species of animal. The examiner is not looking for applicant's disclosure to provide every operable species of mutation detectable by the method claims, but not even a single example is provided.

Conclusion

15. Claims 1-4, 16, 19, 25, 28-37, 39-42, 44, 46-52, 58-61, and 76-78 are free of the prior art with regard to the elected invention. These claims have all been examined as if they require the originally elected primer pairs, SEQ ID NO: 3 and 4 and SEQ ID NO: 19 and 20. Insofar as each of these claims requires the use of SEQ ID NO: 3, the claims are free of the prior art. The closest prior art, exemplified by previously cited Klinger et al. (US 5654170) provides the sequence of the full length PKD1 gene, which comprises instant SEQ ID NO: 3. Klinger et al. also generically teach the selection of oligonucleotides that discriminate the PKD1 gene from PKD1 homologues (see their Col. 5, lines 40-55). Klinger et al. do not provide any specific guidance as to which portions of their SEQ ID NO: 1 would be relevant for selecting polynucleotides with these discriminatory features, nor do Klinger et al. provide the sequence of any PKD1 homologues. The instant specification demonstrates that SEQ ID NO: 3 does in fact provide this specificity (see Example 1). Thus, methods and products which require a primer consisting of instant SEQ ID NO: 3 are free of the prior art. The search and examination has not been extended to the non-elected sequences because a claim has not yet been found allowable.

16. Since SEQ ID NO: 3 has been found to be free of the prior art, applicant is advised that any combination of primers or method of using such a combination of primers with clearly and

specifically requires SEQ ID NO: 3 will be rejoined to the elected invention, if such claims are provided.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is

assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
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Art Unit 1634

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